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 APOPTOSIS
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 L'APOPTOSE
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(21) International Application Number: PCT/EP97/00757 (22) International Filing Date: 18 February 1997 (18.02.97) (30) Priority Data: 522/96 29 February 1996 (29.02.96) CH (71) Applicant (for all designated States except US): NOVARTIS AG [CH/CH]; Schwarzwaldallee 215, CH-4058 Basel (CH). (72) Inventors; and (75) Inventors/Applicants (for US only): DE GASPARO, Marc [CH/CH]; Es Planches 123a, CH-2842 Rossemaison (CH). BULLOCK, Gillian, Rosemary [GB/CH]; Innere Margarethenstrasse 17, CH-4051 Basel (CH). CRISCIONE, Leoluca [IT/CH]; Kirchstrasse 15, CH-4313 Möhlin (CH). (74) Common Representative: NOVARTIS AG; Patent- und Markenabteilung, Lichtstrasse 35, CH-4002 Basel (CH).		(81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: AT ₁ RECEPTOR ANTAGONIST FOR THE STIMULATION OF APOPTOSIS (57) Abstract The invention provides the use of an AT ₁ receptor antagonist, or of a pharmaceutical salt thereof, for producing a pharmaceutical preparation for the stimulation of apoptosis and for the treatment of pathological symptoms which are substantially reduced, halted or prevented by apoptosis, and also corresponding pharmaceutical preparations.		

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AT₁ RECEPTOR ANTAGONIST FOR THE STIMULATION OF APOPTOSIS

The enzyme cascade of the renin-angiotensin system (RAS) comprises a series of biochemical events and, as is well known, there are a variety of approaches for using regulatory intervention to open up treatment possibilities, for example treatment of hypertension.

Angiotensinogen, an α 2-macroglycoprotein, is cleaved by the enzyme renin into the decapeptide angiotensin I, which is itself only very slightly active biologically. In the next step of the cascade, two further amino acids are cleaved off by the action of the enzyme angiotensin converting enzyme (ACE), which is mainly bound in the endothelium, with the formation of angiotensin II. The latter is regarded as being one of the most powerful natural vasoconstrictors.

The vasoconstrictive effects of angiotensin II are brought about by its action on the smooth muscle cells, and by stimulating formation of the adrenergic hormones adrenaline and noradrenaline and by increasing the activity of the sympathetic nervous system due to the formation of noradrenaline. In addition angiotensin II affects the electrolyte balance, generating, for example, antinatriuretic and antiuretic effects in the kidney, and consequently promotes release of the peptide vasopressin from the pituitary, on the one hand, and of aldosterone from the adrenal glomerulosa, on the other. All these effects play an important role in blood pressure regulation.

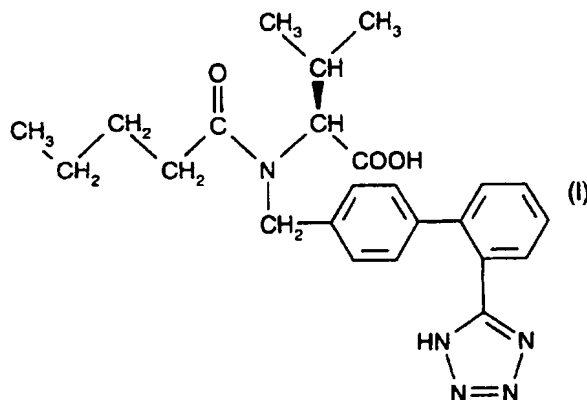
Angiotensin II interacts with specific receptors on the surface of the target cell. Success has by now been achieved in identifying receptor subtypes which are, for example, designated AT₁ receptors and AT₂ receptors. Recently, considerable efforts have been made to identify the substances which bind to the AT₁ receptor, with active compounds of this nature frequently being termed angiotensin II antagonists. As a consequence of the inhibition of the AT₁ receptor, these antagonists can, for example, be employed as antihypertensives or for treating congestive heart failure.

Angiotensin II antagonists are understood to mean those active compounds which bind to the AT₁ receptor subtype. This category includes compounds having differing structural features. For example, mention may be made of the compounds which are listed in the

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European Patent Application having the publication No. 443983 (EP 443983), in particular in the substance claims, the subject-matter of which claims is hereby incorporated into the present application by reference to this publication.

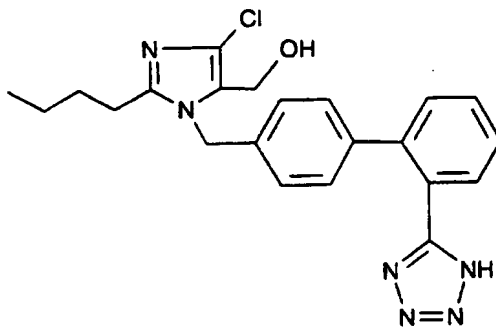
Preference is given to (S)-N-(1-carboxy-2-methylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine [Valsartan] of the formula



and its pharmaceutically utilizable salts.

Furthermore, the compounds which are listed in European Patent Application having the publication No. 253310 (EP 253310), in particular in the substance claims, are hereby incorporated into the present application by reference to this publication.

Preference is given to the compound [Losartan] of the following formula

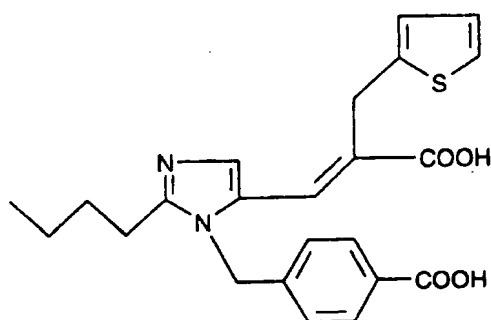


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and its pharmaceutically utilizable salts.

Furthermore, the compounds listed in the European Patent Application having the publication No. 403159 (EP 403159), in particular in the substance claims, are hereby incorporated into the present application by reference to this publication.

Preference is given to the compound [Eprosartan] of the following formula

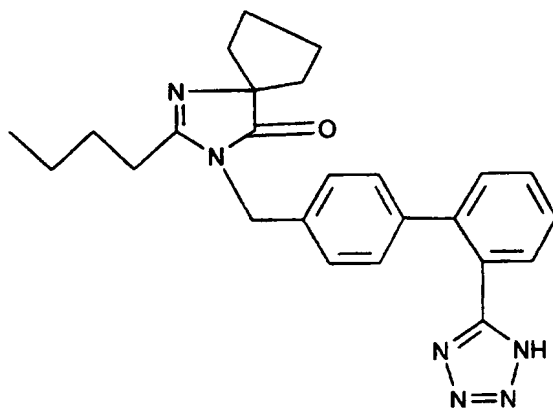


and its pharmaceutically utilizable salts.

Furthermore, the compounds listed in the PCT Patent Application having the publication No. WO 91/14679, in particular in the substance claims, are hereby incorporated into the present application by reference to this publication.

Preference is given to the compound [Irbesartan] of the following formula

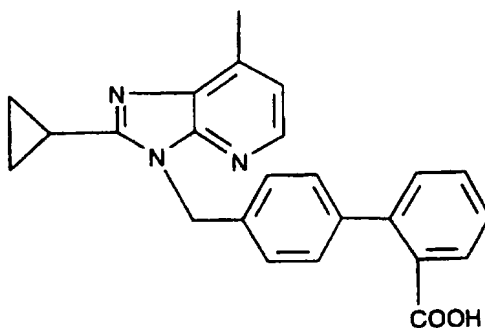
- 4 -



and its pharmaceutically utilizable salts.

Furthermore, the compounds listed in the European Patent Application having the publication No. EP 420237 (EP 420237), in particular in the substance claims, are hereby incorporated into the present application by reference to this publication.

Preference is given to the compound [E-1477] of the following formula

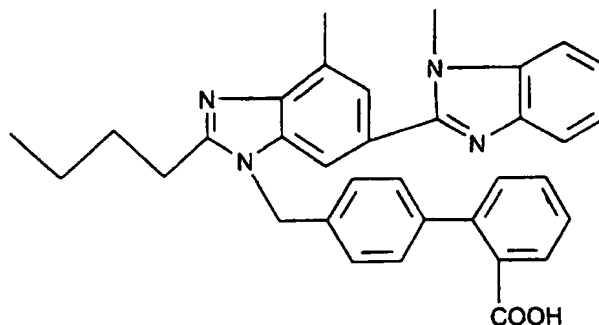


and its pharmaceutically utilizable salts.

Furthermore, the compounds listed in the European Patent Application having the publication No. 502314 (EP 502314), in particular in the substance claims, are hereby incorporated into the present application by reference to this publication.

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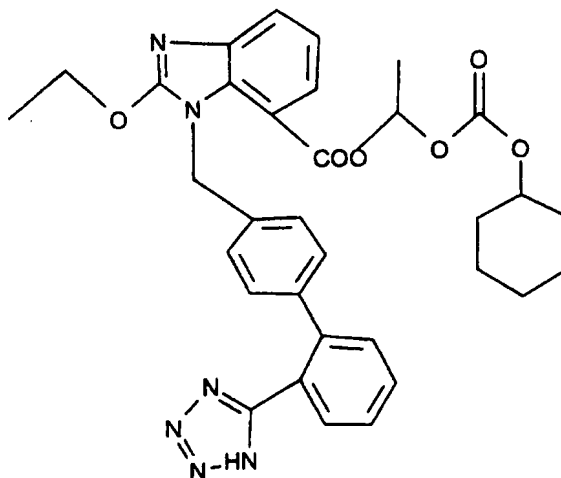
Preference is given to the compound [Telmisartan] of the following formula



and its pharmaceutically utilizable salts.

Furthermore, the compounds listed in the European Patent Application having the publication No. 459136 (EP 459136), in particular in the substance claims, are hereby incorporated into the present application by reference to this publication.

Preference is given to the compound [Candesartan] of the following formula

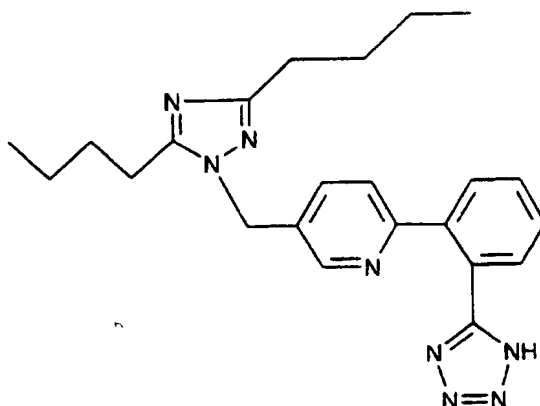


and its pharmaceutically utilizable salts.

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Furthermore, the compounds listed in European Patent Application having the publication No. 504888 (EP 504888), in particular in the substance claims, are hereby incorporated into the present application by reference to this publication.

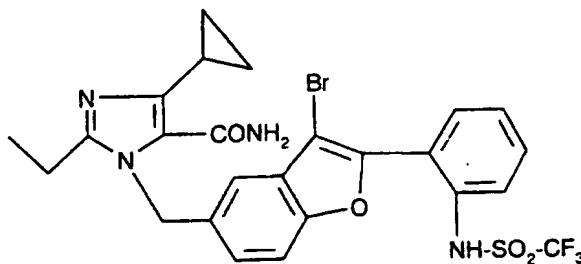
Preference is given to the compound [SC-52458] of the following formula



and its pharmaceutically utilizable salts.

Furthermore, the compounds listed in the European Patent Application having the publication No. 514198 (EP 514198); in particular in the substance claims, are hereby incorporated into the present application by reference to this publication.

Preference is given to the compound [Saprisartan] of the following formula

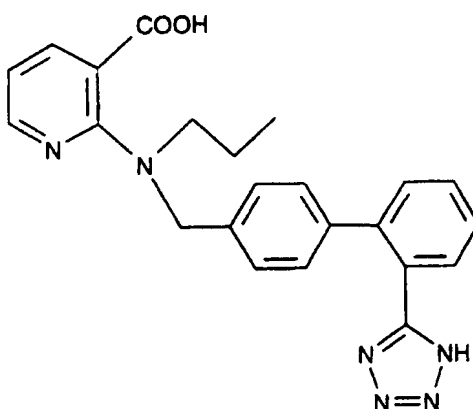


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and its pharmaceutically utilizable salts.

Furthermore, the compounds listed in the European Patent Application having the publication No. 475206 (EP 475206), in particular in the substance claims, are hereby incorporated into the present application by reference to this publication.

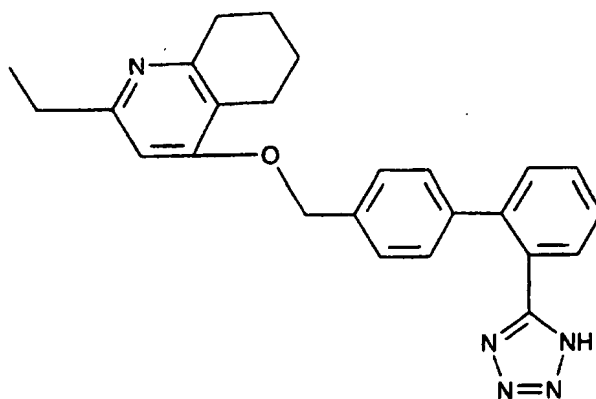
Preference is given to the compound of the following formula



and its pharmaceutically utilizable salts.

Furthermore, the compounds listed in the PCT Patent Application having the publication No. WO 93/20816, in particular in the substance claims, are hereby incorporated into the present application by reference to this publication.

Preference is given to the compound [ZD-8731] of the following formula



and its pharmaceutically utilizable salts.

AT₁ receptor antagonists which, for example, possess at least one basic centre can form acid addition salts. These are formed, for example, using strong inorganic acids, such as mineral acids, e.g. sulfuric acid, a phosphoric acid or a hydrohalic acid, using strong organic carboxylic acids, such as C₁-C₄alkanecarboxylic acids which are unsubstituted or substituted, for example, by halogen, e.g. acetic acid, such as saturated or unsaturated dicarboxylic acids, e.g. oxalic, malonic, succinic, maleic, fumaric, phthalic or terephthalic acid, such as hydroxycarboxylic acids, e.g. ascorbic, glycolic, lactic, malic, tartaric or citric acid, such as amino acids, e.g. aspartic or glutamic acid, or such as benzoic acid, or using organic sulfonic acids, such as C₁-C₄alkanesulfonic acids or arylsulfonic acids which are unsubstituted or substituted, for example, by halogen, e.g. methanesulfonic acid or p-toluenesulfonic acid. Examples of suitable salts with bases are metal salts, such as alkali metal or alkaline earth metal salts, e.g. sodium, potassium or magnesium salts, or salts with ammonia or an organic amine, such as morpholine, thiomorpholine, piperidine, pyrrolidine, a mono-, di- or tri-lower alkyl amine, e.g. ethyl-, tert-butyl-, diethyl-, diisopropyl-, triethyl-, tributyl- or dimethylpropyl-amines, or a mono-, di- or tri-hydroxy lower alkyl amine, e.g. mono-, di- or tri-ethanolamine. Furthermore, corresponding internal salts can be formed.

It has now been found, surprisingly, that AT₁ receptor antagonists stimulate the process of apoptosis.

Apoptosis plays an important role in morphogenesis, in dealing with hormonal and immunological responses and in the homeostatic balance of hypertrophy and atrophy. For example, apoptosis is the physiological mechanism which is involved in ovarian follicular atresia. Consequently, apoptosis is a fundamental physiological homeostatic process in multicellular organisms, playing an important role in the formation, shaping and maintenance of tissues. For example, damaged, precancerous and cancerous cells are eliminated in this process. Apoptosis requires active genetic transcription and translation and is correspondingly subject to genetic or epigenetic control. In this process, various morphological stages are passed through, which stages can generally be used as a base for establishing functional characterization. For example, apoptosis is induced by a signal, separation of adjacent cells takes place and the cytoplasm contracts. Condensation of the chromatin then takes place, followed by a fragmentation into membrane-bound apoptotic bodies. These latter are phagocytosed by neighbouring cells and broken down by the visiting cells using lysosomes. As previously mentioned, this course of events can be followed morphologically by means of monitoring with light microscopy or electron microscopy and also by means of molecular techniques, such as DNA laddering.

In the specialist literature, the term "programmed cell death" is also used synonymously with apoptosis. However, in connection with the present invention, the apoptosis which is evoked by active substances will also be included in addition to the apoptosis which strictly speaking is genetically controlled.

Stimulation of apoptosis by AT₁ receptor antagonists can, for example, be established experimentally as follows:

Eight week-old spontaneously hypertensive rats (SHR) are treated over a period of eight weeks by the daily administration of 10 mg of an AT₁ receptor antagonist, for example Valsartan, per kg. For fixing, the dissected-out femoral artery is rinsed for 10 minutes at a flow rate of 5 ml/min. A solution of 2.5% glutaraldehyde in an 0.1 mole phosphate buffer at pH 7.4 is used as fixative. The temperature of the rinsing solution is 25°C. Following fixation, samples of the artery, each about 2-4 cm in length, are removed. These samples are post-fixed in OsO₄ (1%; 1 hour), dehydrated with alcohols and embedded in epon/araldite. Semi-thin sections of the vessels are cut in the transverse plane, stained for contrast with methylene blue/azure II and checked under a light microscope. The

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corresponding procedure is carried out using non-hypertensive rats (WKY) and hypertensive control animals (spontaneously hypertensive rats - SHR). In three out of 4 animals in each group, sections of the three different regions of the femoral arteries are prepared for light microscopy and/or electron microscopy. These sections are also stained with methylene blue/azure II for contrasting for light microscopy or stained for electron microscopy by treating them with uranyl acetate/lead citrate. The samples are examined in a negative control experiment.

Evaluation of the experiments following administration of Valsartan as compared with each respective control group gives the following result:

Experiment	Animals	Block sections	LM	EM
(i) WKY control	3	9	15	46
(ii) SHR control	4	9	9	60
(iii) SHR+Valsartan	4	9	16	58

[LM= light microscopy; EM= electron microscopy]

The results of the evaluation show the following:

Control tissue (WKY):

The appearance of the endothelium in this tissue is as expected in the case of cells which are tightly bound to the elastic lamina (EL). The EL appears flat with few gaps. In most cases, the smooth muscle cells (SMC) are in a state of disorder, with the cells themselves having a relatively unwrinkled periphery. They do not have the same regular organization as in the case of the Wistar rat, for example, and the WKY rat is therefore to be regarded as differing structurally.

The gap junctions are close together and no irregular changes are apparent.

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SHR Rats:

The blood vessel wall is generally thicker and the endothelium is no longer one single layer of cells, but it is instead replaced by a mixture of cells and collagen which is present between the endothelium and the EL. There are many tears or thinner regions in the lamina.

The gap junctions in the endothelium display extensive invaginations and long tongues on the luminal side.

Valsartan:

Treatment with Valsartan results in a different appearance as compared with that of the controls. It is possible to observe a certain degree of vacuole formation in the endothelial layer, zones containing collagen, extended tracts of still apparent SMC and the occasional appearance of markedly dense cells. It was possible to see these dense SMC cells, which possess large empty vacuoles and which are distributed over the whole of the vessel wall in an irregularly scattered manner, in the light microscope. The nuclei in these cells have a different appearance as compared with those of normal cells, with these dense SMC cells being shrunken and having a very pronounced content of chromatin. Many cells have vacuoles which are filled with amorphous proteinaceous material. This phenomenon corresponds to that which occurs in apoptosis or programmed cell death. While the wall thickness in the regions which appear normal seems to correspond to that of normal cells, the dense cells indicate that the regression of the hypertrophy is still not complete. In some regions, the tissue structure is found to be extremely abnormal, with cell processes which proceed from one cell through the cytoplasm into other cells.

While endothelial gap junctions are not visibly altered, it is possible to observe a slight increase in the separation of the endothelium from the underlying lamina.

The change in the cell wall thickness following treatment with an AT₁ receptor antagonist is very advantageous and must be assumed to be a general feature of the AT₁ receptor antagonist class of active compounds.

Frequency, in per cent, of cell types or cell structures:

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	WKY	SHR	SHR + Valsartan
Very regular cell arrangement	95%	75%	25%
necrotic/hypoxic	-	7%	5%
vacuolated cells	-	-	10%
apoptotic cells	-	-	45%

The results from these investigations unambiguously demonstrate a surprisingly significant appearance of apoptotic cells when hypertensive animals are treated with the AT₁ receptor antagonist Valsartan. Accordingly, it is to be deduced from this that AT₁ receptor antagonists stimulate apoptosis.

Accordingly, AT₁ receptor antagonists can be used in therapeutically effective quantities to stimulate apoptosis and are consequently suitable for the treatment of pathological symptoms which are substantially reduced, halted or prevented by apoptosis.

AT₁ receptor antagonists and their pharmaceutically utilizable salts can, therefore, be used in therapeutically effective quantities for the treatment of vascular proliferation disturbances, including vascular cell wall hypertrophy which follows a thrombosis, angioplasty, Bürger's disease, atherosclerosis and arteriosclerosis.

Apoptosis occurs, for example, in malignant tumours, with the growth of these tumours frequently being retarded. In particular, apoptotic effects are found in increased quantity in tumours which react to irradiation, cytotoxic chemotherapy and hormonal ablation.

In general, substances which stimulate apoptosis can be employed in those cases where there is abnormal cell growth, for example in order to initiate endometrial and prostatic regression (endometriosis, prostate hypertrophy and reduce the size of fat storage cells (obesity)).

Such areas of application lie, for example, in the field of cancer treatment (e.g. in order to suppress unimpeded cell proliferation), in the treatment of immunosuppressive disorders and also in the achievement of resistance to chemotherapies or radiotherapies. Blood

vessels can also be regulated or restored, e.g. following restenosis, by stimulating apoptosis.

The invention provides pharmaceutical preparations, which comprise an AT₁ receptor antagonist or a pharmaceutically utilizable salt thereof, for stimulating apoptosis and for treating pathological symptoms which are substantially reduced, halted or prevented by apoptosis.

The invention also provides the use of an AT₁ receptor antagonist, or a pharmaceutical salt thereof, for producing a pharmaceutical preparation for the stimulation of apoptosis and for the treatment of pathological symptoms which are substantially reduced, halted or prevented by apoptosis.

The invention furthermore provides a process for stimulating apoptosis and for treating pathological symptoms which are substantially reduced, halted or prevented by apoptosis, which comprises administering a therapeutically effective quantity of an AT₁ receptor antagonist or a pharmaceutical salt thereof.

The invention also provides the use of an AT₁ receptor antagonist, or a pharmaceutical salt thereof, for stimulating apoptosis and for treating pathological symptoms which are substantially reduced, halted or prevented by apoptosis.

These pharmaceutical preparations are for enteral, such as oral, and also rectal or parenteral, administration to homeotherms, with the preparations comprising the pharmacological active compound either alone or together with customary pharmaceutical auxiliary substances. For example, the pharmaceutical preparations consist of from about 0.1 % to 100 %, preferably of from about 1 % to about 80 %, of the active compound. Pharmaceutical preparations for enteral or parenteral, and also for ocular, administration are, for example, in unit dose forms, such as coated tablets, tablets, capsules or suppositories and also ampoules. These are prepared in a manner which is known per se, for example using conventional mixing, granulation, coating, solubilizing or lyophilizing processes. Thus, pharmaceutical preparations for oral use can be obtained by combining the active compound with solid excipients, if desired granulating a mixture which has been

obtained, and, if required or necessary, processing the mixture or granulate into tablets or coated tablet cores after having added suitable auxiliary substances.

Suitable excipients are, in particular, fillers, such as sugars, for example lactose, sucrose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, and also binders, such as starch pastes, using, for example, maize starch, wheat starch, rice starch or potato starch, gelatin, gum tragacanth, methyl cellulose and/or polyvinylpyrrolidone, and, if desired, disintegrants, such as the abovementioned starches, and also carboxymethyl starch, crosslinked polyvinylpyrrolidone, agar or alginic acid or a salt thereof, such as sodium alginate. Adjuvants are first and foremost flow-regulating agents and lubricants, for example silicic acid, talc, stearic acid or salts thereof, such as magnesium, or calcium stearate, and/or polyethylene glycol. Coated tablet cores are provided with suitable coatings which may or may not be resistant to gastric juice, with use being made, inter alia, of concentrated sugar solutions, which, if desired, comprise arabic gum, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, lacquer solutions in suitable organic solvents or solvent mixtures, or, for preparing coatings which are resistant to gastric juice, solutions of suitable cellulose preparations, such as acetyl cellulose phthalate or hydroxypropylmethyl cellulose phthalate. Dyes or pigments can be added to the tablets or coated tablet coatings, for example for the purpose of identifying or labelling different active compound doses.

Further pharmaceutical preparations which can be used orally are hard capsules made of gelatin and also soft, closed capsules made of gelatin and an emollient, such as glycerol or sorbitol. The hard capsules can comprise the active compound in the form of a granulate, for example admixed with fillers such as lactose, binders, such as starches, and/or glidants, such as talc or magnesium stearate, and, if desired, stabilizers. In soft capsules, the active compound is preferably dissolved or suspended in suitable liquids, such as fatty oils, paraffin oil or liquid polyethylene glycols, with it being possible to add stabilizers in this case as well.

Examples of suitable pharmaceutical preparations which can be used rectally are suppositories which consist of a combination of the active compound and a suppository groundmass. Examples of suitable suppository groundmasses are natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols and higher alkanols. In addition,

gelatin rectal capsules can also be used which comprise a combination of the active compound and a groundmass substance. Examples of suitable groundmass substances are liquid triglycerides, polyethylene glycols and paraffin hydrocarbons.

Aqueous solutions of an active compound in water-soluble form, for example of a water-soluble salt, and also suspensions of the active compound, such as appropriate oily injection suspensions, with suitable lipophilic solvents or vehicles, such as fatty oils, for example benne oil, or synthetic fatty acid esters, for example ethyl oleate or triglycerides, being used, or aqueous injection suspensions which combine viscosity-increasing substances, for example sodium carboxymethyl cellulose, sorbitol and/or dextran, and, if desired, stabilizers as well, are most suitable for parenteral administration.

The dosage of the active compound can depend on a variety of factors, such as mode of administration, homeothermic species, age and/or individual condition. Normally, in the case of oral administration, an approximate daily dose of from about 10 mg to about 250 mg, for example in the case of Valsartan of about 40 mg, 80 mg or 160 mg, is to be estimated for a patient of approximately 75 kg in weight.

The following example illustrates the above-described invention; however, it is not intended to restrict the scope of this invention in any manner.

Formulation Example 1:

A hard gelatin capsule which, for example, comprises (S)-N-(1-carboxy-2-methylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine, as the active compound can, for example, be of the following composition:

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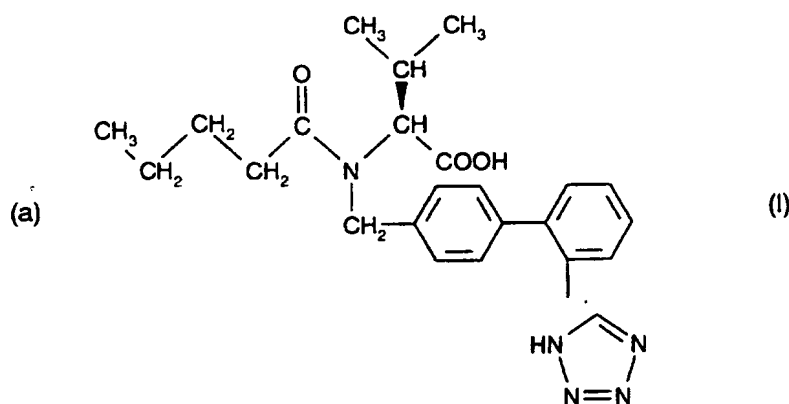
Composition:

(1) Active compound	80.0 mg
(2) Microcrystalline cellulose	110.0 mg
(3) Polyvidone K30	45.2 mg
(4) Sodium lauryl sulfate	1.2 mg
(5) Crospovidone	26.0 mg
(6) Magnesium stearate	2.6 mg

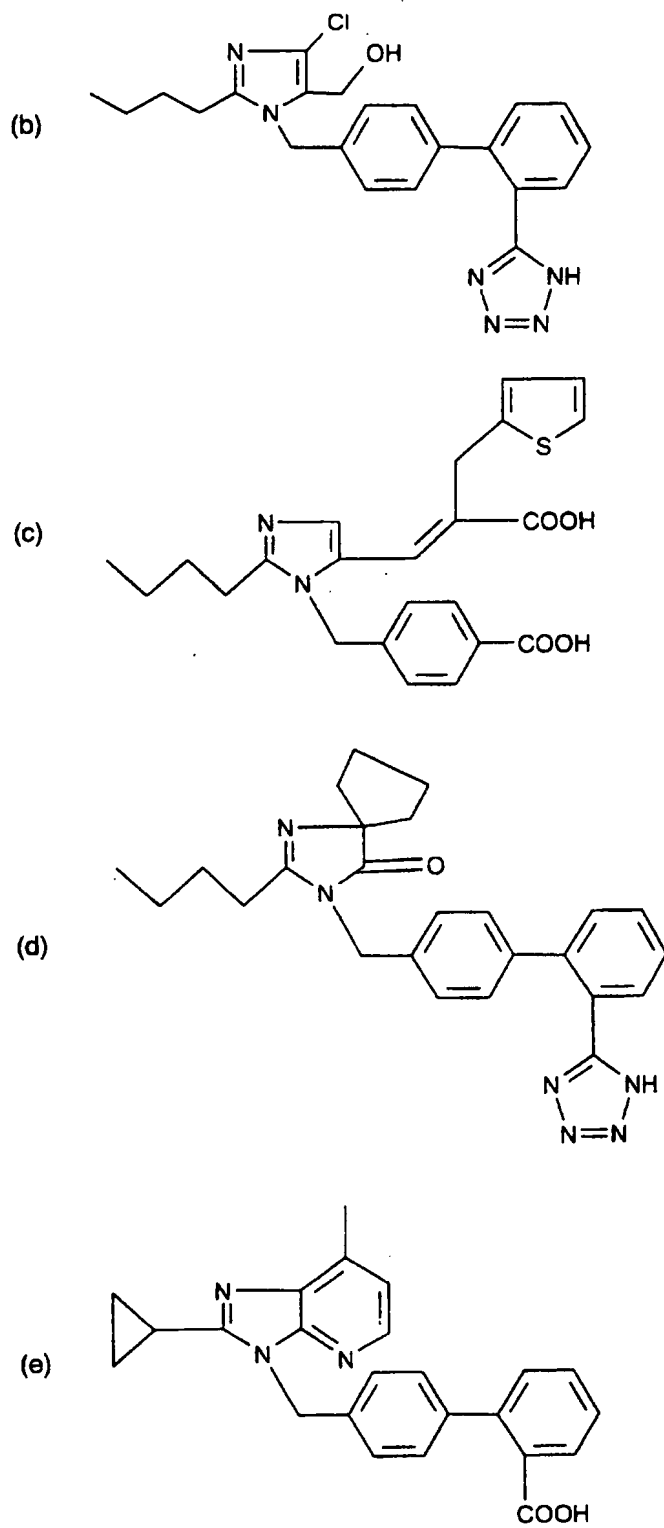
Components (1) and (2) are granulated together with a solution of components (3) and (4) in water. Components (5) and (6) are added to the dry granulate and the whole is used to fill size 1 hard gelatin capsules.

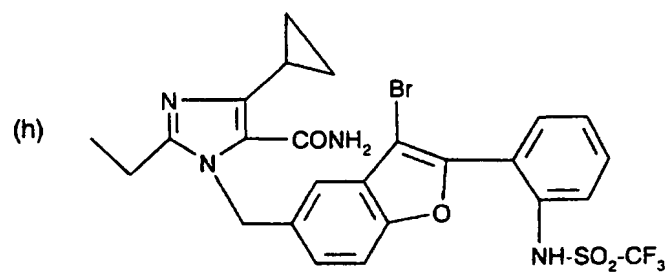
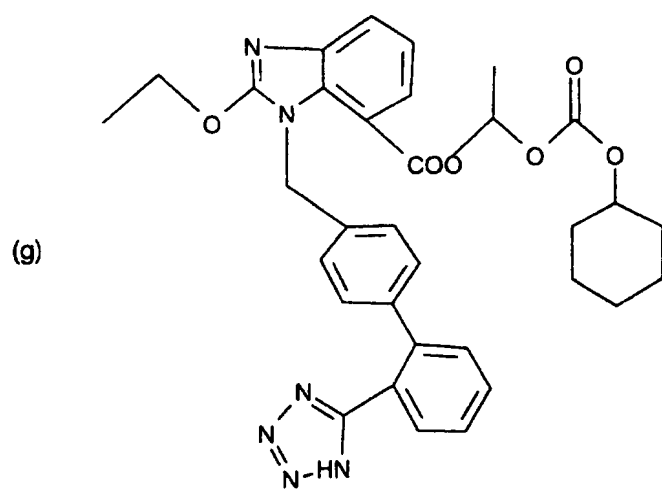
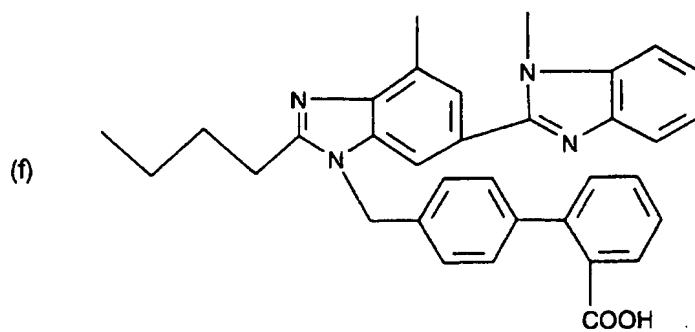
What is claimed is:

1. The use of an AT₁ receptor antagonist, or of a pharmaceutical salt thereof, for producing a pharmaceutical preparation for the stimulation of apoptosis and for the treatment of pathological symptoms which are substantially reduced, halted or prevented by apoptosis.
2. A pharmaceutical preparation for the stimulation of apoptosis and for the treatment of pathological symptoms which are substantially reduced, halted or prevented by apoptosis, which comprises an AT₁ receptor antagonist or a pharmaceutical salt thereof.
3. A process for stimulating apoptosis and for treating pathological symptoms which are substantially reduced, halted or prevented by apoptosis, which comprises administering a therapeutically effective quantity of an AT₁ receptor antagonist or a pharmaceutical salt thereof.
4. The use of an AT₁ receptor antagonist, or of a pharmaceutical salt thereof, for stimulating apoptosis and for treating pathological symptoms which are substantially reduced, halted or prevented by apoptosis.
5. The use according to claim 1 or 4, wherein a compound which is selected from the group consisting of:

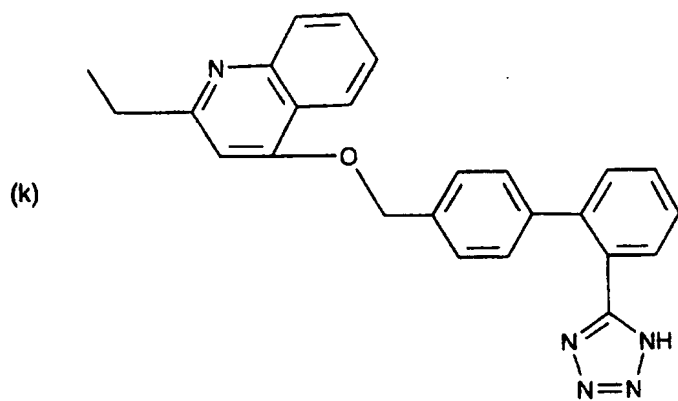
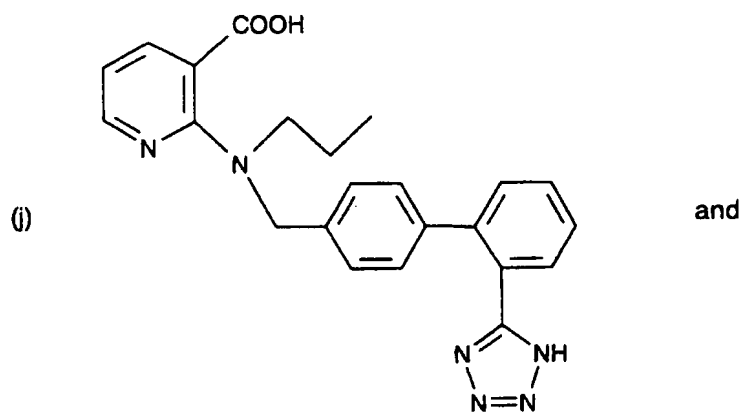
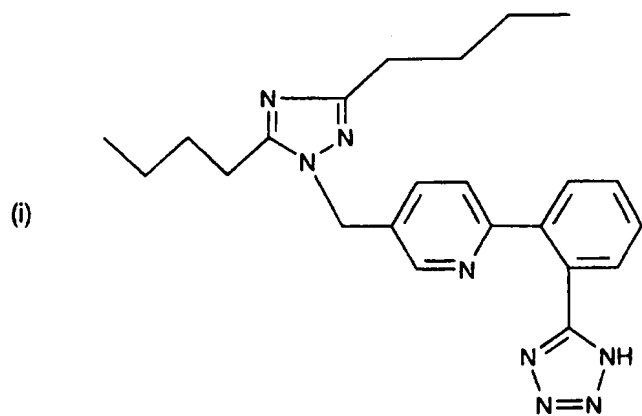


- 18 -



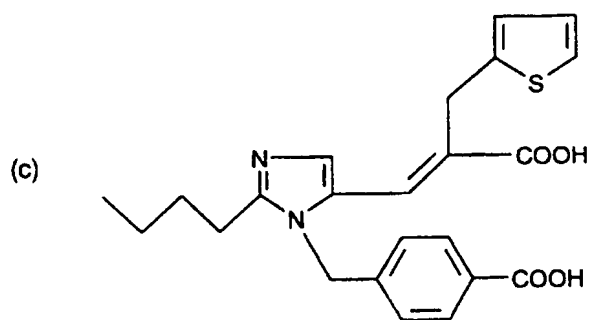
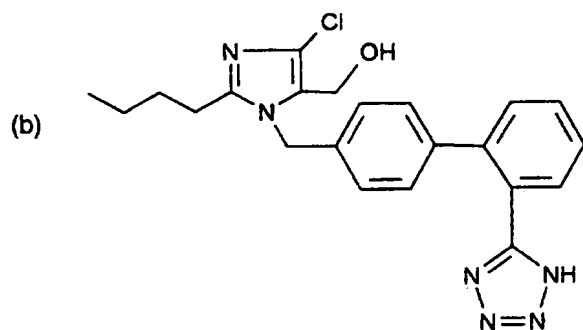
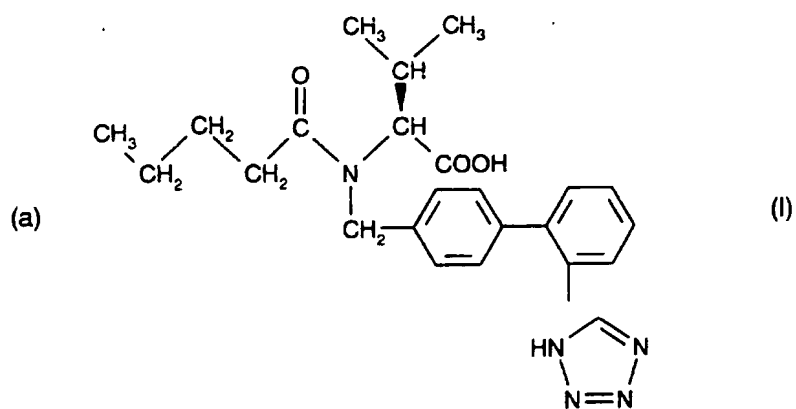


- 20 -

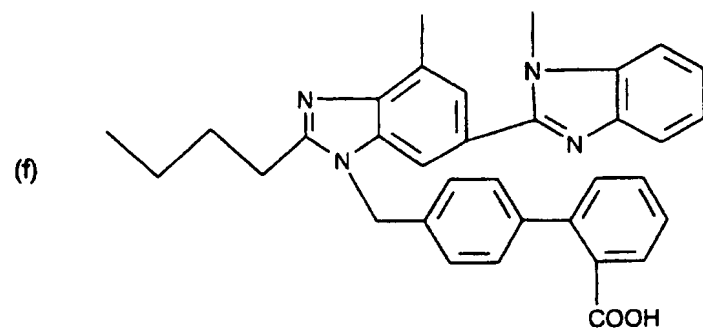
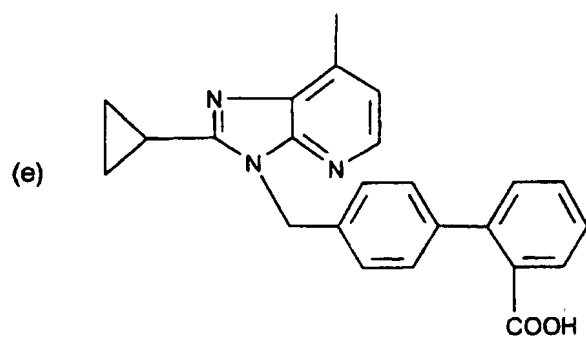
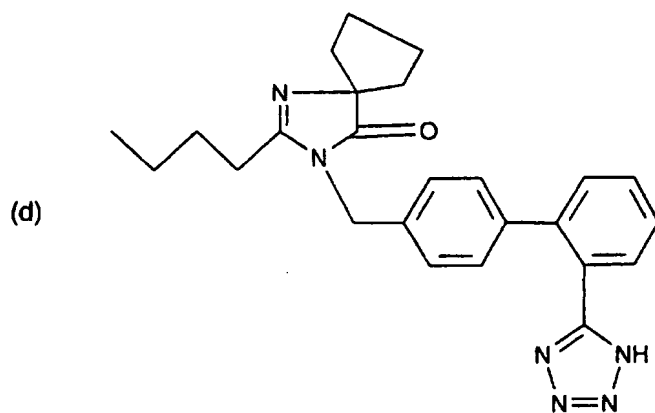


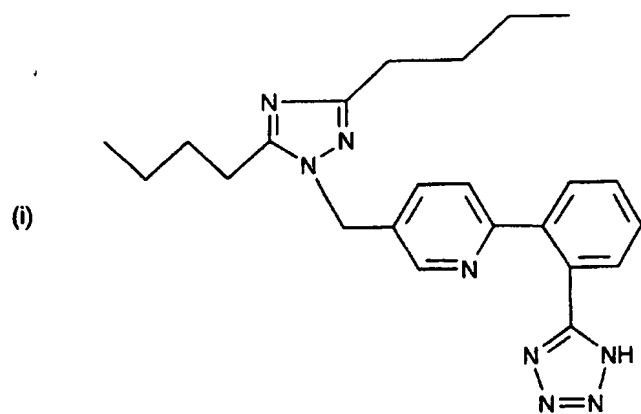
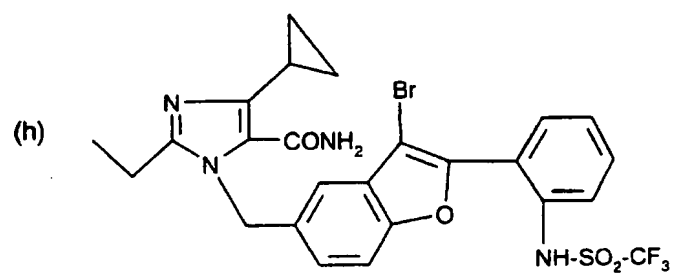
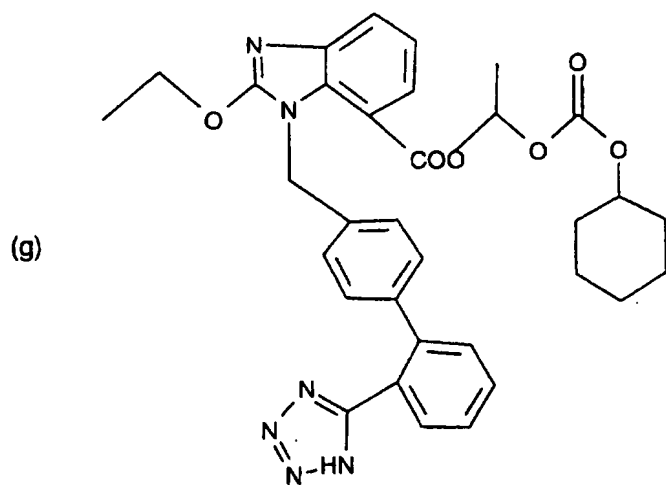
or in each case a pharmaceutically utilizable salt thereof, is suitable for use as the AT₁ receptor antagonist.

6. A process according to claim 3 for treating pathological symptoms which are substantially reduced, halted or prevented by apoptosis, wherein a therapeutically effective quantity of an AT₁ receptor antagonist selected from the group consisting of:

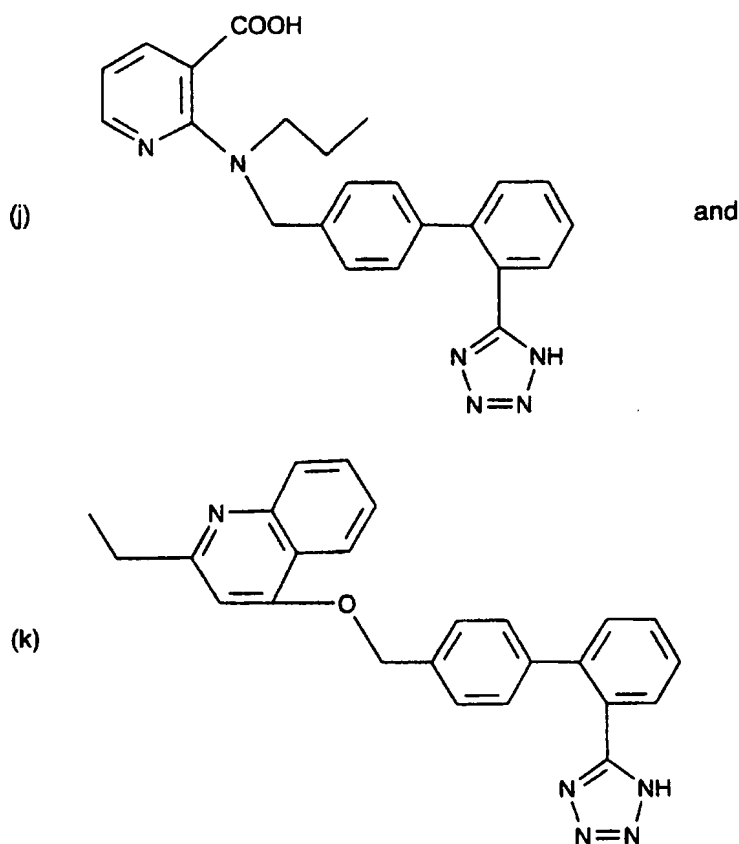


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or in each case a pharmaceutically utilizable salt thereof, is employed.

7. The use of an AT₁ receptor antagonist according to claim 1 or 5 for producing a pharmaceutical preparation for the suppression of unimpeded cell proliferation, for the treatment of endometriosis, prostate hypertrophy, obesity, immunosuppressive disorders and restenosis, and for achieving resistances to chemotherapies and radiotherapies.

8. A pharmaceutical preparation according to claim 2 for producing a pharmaceutical preparation for the suppression of unimpeded cell proliferation, for the treatment of endometriosis, prostate hypertrophy, obesity, immunosuppressive disorders and restenosis, and for achieving resistances to chemotherapies and radiotherapies.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 97/00757

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/41 A61K31/44 A61K31/47

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BLOOD PRESS. SUPPL., vol. 5, 1994, pages 38-42, XP000674563 TAGUCHI ET AL: "topical application of AT1 receptor antagonists prevents medial and neointimal proliferation after balloon injury" see the whole document ---	1,2,5,7, 8
X	J CARDIOVASC PHARMACOL, vol. 23, no. 2, 1994, pages 175-179, XP000674560 KOH ET AL: "effects of an angiotensin II receptor antagonist CV-11974 on angiotensin II-induced increases in calcium concentration, hyperplasia and hypertrophy of CVSMC" see the whole document ---	1,2,5,7, 8
-/--		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

5 June 1997

Date of mailing of the international search report

20.06.97

Name and mailing address of the ISA

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Authorized officer

Trifilieff-Riolo, S

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 97/00757

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>GENERAL PHYSIOLOGY AND BIOPHYSICS, vol. 14, no. 5, 1995, pages 383-391, XP000674561 ZORAD ET AL: "the role of angiotensin II and its receptors in regulation of adipose tissue metabolism and cellularity" see abstract see page 388, line 8-9 ---</p>	1,2,5,7, 8
X	<p>J PHARMACOL EXP THER, vol. 266, no. 3, 1993, pages 1664-1669, XP000674558 KAWAMURA ET AL: "CV-116 a novel angiotensin II receptor antagonist..." see the whole document ---</p>	1,2,5,7, 8
X	<p>EUR J PHARMACOL, vol. 251, no. 2,3, 1994, pages 143-150, XP000674536 HERBERT ET AL: "effect of SR 47436 on human vascular smooth muscle cells in vitro" see the whole document ---</p>	1,2,5,7, 8
X	<p>US 5 250 548 A (WINN MARTIN ET AL) 5 October 1993 cited in the application corresponds to EP 475206 cited on p. 7 see column 1, line 14 see claim 5 -----</p>	1,2,5,7, 8

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 97/00757

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 3,4,6
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 3,4,6
is(are) directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 97/00757

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5250548 A	05-10-93	AU 647174 B	17-03-94
		AU 8374491 A	12-03-92
		CA 2050723 A	11-03-92
		EP 0475206 A	18-03-92
		JP 7053551 A	28-02-95
		JP 4261156 A	17-09-92
		US 5210206 A	11-05-93
		US 5284954 A	08-02-94
